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DOI:

[10.1016/j.urolonc.2017.07.018](https://doi.org/10.1016/j.urolonc.2017.07.018)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Lee, S-M., Liyanage, S. H., Wulaningsih, W., Wolfe, K., Carr, T., Younis, C., Van Hemelrijck, M., Popert, R., & Acher, P. (2017). Toward an MRI-based nomogram for the prediction of transperineal prostate biopsy outcome: A physician and patient decision tool. *UROLOGIC ONCOLOGY*. <https://doi.org/10.1016/j.urolonc.2017.07.018>

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**Towards a MRI-based nomogram for the prediction of transperineal prostate biopsy
outcome: a physician and patient decision tool**

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Keywords: Magnetic Resonance Imaging; Nomogram; Prostate Biopsy; Prostate Cancer; Risk Assessment

Funding: This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Conflicts of Interest: None disclosed.

Abstract:

Purpose: To develop and internally validate a nomogram utilising biparametric magnetic resonance imaging (B-MRI)-derived variables for the prediction prostate cancer at transperineal sector-guided prostate biopsy (TPSB).

Subjects/Patients and Methods: Consecutive patients referred to our institution with raised PSA, abnormal prostate examination or persistent suspicion of prostate cancer after previous transrectal biopsy between July 2012 and November 2015 were reviewed from a prospective database.

All patients underwent pre-biopsy B-MRI with T2-weighted and diffusion-weighted imaging sequences, followed by 24-40 core TPSB with additional targeted cores using cognitive registration.

Univariable and multivariable logistic regression analysis was used to determine predictors of prostate cancer outcomes. Multivariable coefficients were used to construct two MRI-based nomograms to predict any and significant (Gleason 4 or Maximum Cancer Core Length ≥ 6 mm) prostate cancer at TPSB. Bootstrap resamples were used for internal validation. Accuracy was assessed by calculating the concordance index (c-index).

Results: In total, 615 men were included in the study. Prostate cancer was diagnosed in 317 (51.5%) men with significant cancer diagnosed in 237 (38.5%) men.

Age, PI-RADS score, PSA, PSA Density (PSAD) and Primary Biopsy were predictors of prostate cancer at TPSB on univariable analysis ($p < 0.0001$). PSA showed strong correlation with PSAD and was excluded. The remaining variables were all independent predictors of prostate cancer on multivariable analysis ($p < 0.0001$) and used to generate the nomograms.

Both nomograms showed good discrimination for prostate cancer, with a c-index of 87% for any cancer and 92% for significant disease. Using a nomogram-derived probability threshold of <15%, 111 (18.0%) of biopsies can be saved, at the expense of 3 missed significant prostate cancers.

Conclusions: These internally-validated MR-based nomograms were able to accurately predict TPSB outcomes for prostate cancer, especially significant disease. Our findings support the combination of pre-biopsy MRI results and clinical factors as part of the biopsy decision-making process.

Introduction

In current practice, men suspected of harbouring prostate cancer undergo initial transrectal prostate biopsy based upon abnormal digital rectal examination (DRE) or raised prostate specific antigen (PSA). Of these biopsies, only 40% will be positive, and detection rates of subsequent biopsies fall below 20% [1-4].

Multiple factors underlie this low detection rate. Serum PSA is used for screening, but, by itself cannot accurately distinguish between benign and malignant conditions, contributing to poor detection rates [5]. Furthermore, a proportion of cancers detected through PSA screening will be small volume, low-risk disease that may not require treatment [5].

Transrectal biopsies also suffer from anatomical limitations. Random needle biopsy often leads to sampling error due to heterogeneity within prostate tumours, resulting in misdiagnosis [6]. As the prostate is approached posteriorly via the rectum, specific anatomical areas are undersampled. The anterior aspect of the prostate is challenging to biopsy, while the detection of apical tumours is limited by the needle angle attainable through the rectum [7, 8].

In addition to poor detection rates, men undergoing transrectal biopsy are placed at risk of biopsy-associated morbidity. The Prostate Biopsy Effects (ProBE) study, nested within the Prostate Cancer for Testing and Treatment (ProtecT) study, gives insight into this; pain is reported by 44%, fever by 18% and haematuria by 66%, with 1.3% requiring hospital admission [9]. One-fifth of men would consider repeat biopsies a moderate to major problem [9]. Improvements to current prostate cancer risk assessments would reduce unnecessary biopsies and morbidity.

The prostate biopsy decision-making process is complex. Tools that provide accurate risk analysis can aid the clinician and patient when considering whether to undertake biopsy. Previously reported biopsy nomograms, based on clinical variables have demonstrated predictive accuracies of only 65-77% [10, 11]. Novel diagnostic parameters can improve on the low PSA sensitivity and optimise the predictive accuracy of these nomograms. As magnetic resonance imaging (MRI) technology has improved through the use of additional sequences, including diffusion-weighted imaging (DWI) and dynamic contrast enhancement (DCE), it is increasingly being used within the diagnostic pathway for prostate cancer [12-14]. The recent Prostate MRI Imaging Study (PROMIS) confirmed multiparametric MRI (T2-weighted, DWI, DCE) to be a useful triage test, with greater sensitivity (93%) as compared to transrectal biopsy (48%) [15]. Since the results of this trial were released, the role of pre-biopsy MRI has been increasing within the United Kingdom, placing increased pressure on radiology departments [16]. Biparametric MRI (B-MRI) represents a valid alternative to mpMRI, with its shorter acquisition times, and we have validated its accuracy previously [13].

Furthermore, PSA density (PSAD) has had potential to improve serum PSA specificity whilst preserving sensitivity. Despite this, use in clinical practice is limited and poor uptake may be related to the use of transrectal ultrasound for prostate volume estimation and transrectal biopsy as the reference standard, two techniques subject to human error and inaccuracy [7, 8, 17]. Separate volume assessments are expensive, inconvenient and uncomfortable for patients. With pre-biopsy MRI, prostate volume can be accurately and conveniently assessed prior to biopsy [18].

In the present study, we aimed to develop a new nomogram, utilising both clinical and biparametric MRI (B-MRI) data for the predicting the presence of cancer on prostate biopsy.

Patients and Methods

The study was approved by the local governance committee as a prospective audit and conforms to the Standards for the Reporting of Diagnostic Accuracy (STARD).

Patient Population

Consecutive patients referred to our institution for biparametric MRI (B-MRI) and transperineal sector-guided prostate biopsy (TPSB) between July 2012 and November 2015 were reviewed from a prospectively-collected database. Referral reasons included raised PSA, abnormal DRE, or persistent suspicion of prostate cancer after previous transrectal biopsy. Patients excluded included: those unable to undergo B-MRI (n=29), B-MRI older than 6 months before biopsy (n=38) or undertaken at other institutions (n=67) and those undergoing active surveillance (n=68).

Biparametric MRI (B-MRI)

All patients underwent B-MRI prior to biopsy and at least 6 months after previous biopsy or prostate instrumentation to avoid haemorrhage artefact. B-MRI was undertaken using a 1.5 Tesla machine (Signa Excite, GE Healthcare, Little Chalfont, UK) and 8-channel phased array body coils. Protocol included axial oblique, sagittal and coronal T2-weighted imaging and axial DWI (Supplementary Table 1). DWI sequences were obtained with b-values of 0, 700 and 1000 in 18 patients, 0, 1000 and 1400 in 26 patients and 0 and 1400 in 571 patients. High b-value images and apparent diffusion coefficient maps were used for analysis.

Reporting was performed by a single urologist (S.H.L.) with 5 years prostate MRI experience and blinded to clinical details. Images were reported using Prostate Imaging

Reporting and Data System (PI-RADS) v1, indicating likelihood of malignancy from 1 to 5 [19]. PI-RADS reporting at our institution has been previously described [13]. Analysis was based upon the highest overall score reported for either B-MRI sequence (T2 or DWI). Final report did not influence the decision to proceed to biopsy for the initial 400 cases. Subsequent patients with negative MRIs, i.e. PI-RADS 1 or 2, were given the option to proceed to biopsy.

Prostate volume was determined with T2-weighted images, using the ellipsoid method, defined as $\pi/6 \times \text{length} \times \text{width} \times \text{height}$. PSAD was defined as total serum PSA divided by prostate volume.

Transperineal Prostate Biopsy

TPSB was performed as previously described [20, 21], preferentially targeting the peripheral zone. The PZ was divided into anterior, mid and posterior sectors for each lobe, and the mid and posterior sectors occupying the PZ posterior to the prostatic urethra, verumontanum and bladder neck. In glands <30ml, four cores were taken from each sector, yielding 24 cores. In glands >30ml, basal biopsies were taken via the mid and posterior sectors to sample the central zone at the base (on either side of the midline), whilst avoiding the TZ. In prostates >50ml, 38 cores were taken: 5 per sector, with 8 basal biopsies. In patients with suspicious MRI lesions, a further 2-4 cores were taken using cognitive registration. The use of TPSB provided a comprehensive reference standard, allowing for accurate prostate cancer diagnosis.

Two outcomes were assessed, any cancer and significant prostate cancer, defined as:

presence of Gleason pattern 4 or maximum cancer core length (MCCL) of $\geq 6\text{mm}$. This core

length was chosen as it corresponded to a lesion volume of 0.5ml, below the calculated threshold of 1.3ml for significant tumour volume [14].

Data Analysis

Data analysis was performed using R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Patient characteristics were compared using chi-squared tests and independent sample t-test for categorical and continuous variables, respectively. Odds ratios (OR) and 95% confidence intervals (95% CI) for any and significant prostate cancer were estimated by univariable logistic regression analysis assessing age, PSA, PSAD, PI-RADS score and primary biopsy as potential predictors. Multivariable logistic regression analysis including all potential predictors was used to determine independent predictors of prostate cancer outcomes. A further sensitivity analysis was performed including only the first 400 patients, as subsequent MRI results were used in the decision-making process in subsequent patients.

A nomogram was developed using the rms package based on the final logistic regression model to estimate the risk of being diagnosed with each prostate cancer outcome.

Performance was evaluated through internal validation, performed by generating 200 bootstrap samples. Nomogram discrimination was assessed by calculating the concordance index (c-index) from the bootstrap samples. A value of 0.5 indicated that 50% of the patients were correctly classified. Calibration curves were generated for the actual and bootstrap samples, demonstrating prediction model accuracy. Various nomogram probability cut-offs were tested to assess the ability to identify patients with and without prostate cancer.

Results

From July 2012 to November 2015, 817 men undergoing TPSB were considered for the study. After exclusions, 615 patients were included, including: patients undergoing primary biopsy for raised PSA or abnormal DRE (n=484) and patients with previous negative transrectal prostate biopsy and ongoing suspicion of prostate cancer (n=131).

Patient characteristics are shown in Table 1 after stratification according to presence and absence of prostate cancer. Overall, 51.5% of the men (n=317) were diagnosed with prostate cancer. Of these, 38.5% (n=237) had significant prostate cancer. 28% (n=175) of patients had negative MRIs (PI-RADS 1 or 2), whereas 51% (n=312) were deemed positive (PI-RADS 4 or 5). In total, 34 (5.5%) patients suffered complications from TPSB, consisting of: 23 (3.7%) episodes of urinary retention, 8 (1.3%) patients with significant haematuria with clots, 1 (0.2%) case of wound bleeding, 1 (0.2%) prostatitis, and 1 (0.2%) patient with SVT following general anaesthetic.

On univariable analysis (Table 2), age, PSA, PSAD, PI-RADS score and primary biopsy were all significant predictors of any and significant prostate cancer at TPSB. A strong correlation between PSA and PSAD density was noted ($r=0.81$), indicating potential collinearity; therefore, PSA was excluded from multivariable analysis. Multivariable logistic regression analysis (Table 2) showed the remaining variables remained independent predictors of both outcomes.

After the first 400 patients, patients were given the informed choice to proceed to biopsy based upon the B-MRI results. Therefore, a further sensitivity analysis was performed,

including only the first 400 patients. Similar albeit slightly weaker findings were observed with all associations remaining statistically significant apart from age (data not displayed).

Using age, PSAD, PI-RADS score and primary biopsy, a nomogram was developed to predict any prostate cancer, as shown in Figure 1. An additional nomogram for the prediction of significant prostate cancer is demonstrated in Figure 2. We ran an additional multivariable analysis for each outcome, using PSA and volume separately. We compared the fit between this and the PSAD model, using analysis of covariance and found that the model using PSAD had significantly greater reduction in the residual sum of squares ($p < 0.05$), indicating a better fit, for all outcomes. Therefore the final model was performed using PSAD.

The nomograms were internally validated using 200 bootstrap samples; calibration curves are shown in Figure 1(b) for any prostate cancer and Figure 2(b) for significant prostate cancer. The c-index for the any prostate cancer nomogram was 0.87 (95% CI 0.84-0.90). For significant prostate cancer, the c-index was 0.92 (95% CI 0.89-0.94).

Finally, Table 3 shows the numbers of biopsies performed and the number of missed prostate cancers at various 'any cancer' probability scores as calculated by our MR-based any prostate cancer nomogram. Sensitivity, specificity, positive predictive values and negative predictive values for significant cancer are also demonstrated at each cut-off value. By utilising this calculator, at a calculated probability cut-off of 5%, 23 (3.7%) biopsies would be avoided, at the expense of 1 missed significant prostate cancers. At a cut-off as high as 30%, 213 (34.6%) biopsies would be avoided, with 6 missed significant prostate cancers.

Discussion

Nomograms for prostate cancer risk assessment based on clinical, laboratory and ultrasound parameters have attempted to improve detection rates and reduce unnecessary biopsies. However, accuracy has been limited and additional prognostic variables can improve their performance [10, 11]. We present nomograms, incorporating MRI-derived and clinical information for the prediction of prostate cancer on TPSB. Internal validation showed strong discrimination with a c-index of 0.87 for any cancer and 0.92 for significant prostate cancer.

The use of MRI has progressed from staging to detection and localisation of tumours [12]. The addition of functional sequences has led to accurate prostate cancer localisation, which can be used in risk stratification before biopsy and studies have shown the sensitivity of mpMRI to be over 90% [12, 15]. The role of prostate MRI has been increasing within the United Kingdom, placing demand on radiology departments, due to the long acquisition times, particularly for DCE sequences [16]. Our MRI index test uses two straightforward, resource-friendly sequences: T2-weighted and DWI sequences. These sequences are widely available, and the lack of DCE reduces sequence times, representing a practical solution to many hospitals.

We have previously validated our B-MRI protocol with the use of PI-RADS scoring [13]; when PI-RADS 1 and 2 lesions were deemed negative, B-MRI had a sensitivity of 97% and specificity of 60% for significant prostate cancer (Gleason pattern 4 or MCCL ≥ 6 mm). These compare favourably to the values reported by the PROMIS study. Ahmed et al. reported mpMRI images using a validated Likert system; again, when Likert 1 and 2 lesions were negative, the authors demonstrated a sensitivity of 87% and specificity of 47% for significant prostate cancer (UCL definition 1: Gleason $\geq 3+4$ or MCCL ≥ 4 mm) [15]. Furthermore, a recent

study by Thestrup et al. [22] showed similar prostate cancer detection rates between B-MRI (sensitivity 0.94-0.96) vs mpMRI (sensitivity 0.93-1.0) across 2 independent readers.

Pre-biopsy imaging also lends itself well to MRI-derived PSAD, which has been demonstrated to more accurately predict TPSB outcomes compared to PSA alone [18, 23]. Given that certain prostate cancers are MRI invisible, inclusion of PSAD within our nomogram aids in the identification of patients harbouring MRI-invisible cancers.

For our reference standard, we used TPSB with its high overall detection rate [13, 24]. This arises from the approach used: by entering the prostate through the skin, systematic investigation of the prostate may be achieved, including the anterior and apical aspects, two areas which are difficult to sample through the transrectal approach [7, 8]. We aimed to provide comprehensive a reference standard as possible, and short of radical prostatectomy, our view is that TPSB provides this. Cognitive-guided cores were included, which are widely available to clinicians and avoid the variability associated with different fusion biopsy systems [25].

These nomograms for prostate cancer may prove to be a valuable patient and clinician decision making tool, potentially avoiding unnecessary biopsies and reducing adverse events, through improved prostate cancer prediction. At a probability cut-off of 5% for any prostate cancer, 27 out of 615 biopsies could be avoided, at the expense of 4 missed prostate cancers, of which 1 is significant. At 10%, this increases to 65 saved biopsies and 11 missed prostate cancers, 2 of which are significant. The acceptability of these missed cancers is open to debate, given the morbidity associated with prostate biopsy.

Table 4 gives an example case of a 60-year old man undergoing primary biopsy. Risk of significant and any (in parentheses) prostate cancer is shown and stratified into categories: low (<5%), medium (5-15%) and high risk (>15%). This example highlights the utility of both MRI and PSAD in establishing prostate cancer risk. Patients falling into lower risk categories may choose to avoid prostate biopsy. These men would continue to undergo surveillance through repeat PSA tests, only proceeding to biopsy when a chosen PSA threshold was reached.

Previous studies have looked at the use of both mpMRI and PSAD for the prediction of prostate cancer. Van Leeuwen et al. [26] developed a predictive model from 393 patients for the prediction of prostate cancer utilising similar variables including PI-RADS v1, with a similar transperineal biopsy reference standard (median 30 cores). The study benefits from a multicentre cohort and retrospective external validation, but demonstrates slightly lower accuracy to our model (AUC 0.80 for any cancer, 0.88 for significant cancer). This may arise from the differing biopsy strategy used during validation (transrectal or transperineal, median 18-cores).

Distler et al. [27] studied the value of adding PSAD to pre-biopsy mpMRI in 1040 men undergoing transperineal biopsy, developing a nomogram utilising these two variables. Accuracy of the nomogram was lower (AUC 0.79) than that seen in this study. In a further study by Radtke et al, of the same study group, risk models for prostate cancer were developed utilising clinical (age, DRE, PSA, volume) and PI-RADS v1 scores [28]. The authors reported good accuracy with 0.83 ROC area under the curve. It is interesting to note that within the latest risk model, the PI-RADS score accounts for fewer overall points as

compared to our model. Both the Van Leeuwen and Radtke nomograms, as well as the present study require prospective external validation.

In a separate large study, Wang et al. [29] examined the value of pre-biopsy MRI in a cohort of 985 Chinese patients, developing a nomogram utilising mpMRI and clinical information for the prediction of prostate cancer over a 2-year follow-up period. This was internally validated showing greater accuracy (AUC 0.938). Despite this, a major shortcoming in the study was the reference standard, which varied considerably, including transrectal biopsy, transurethral resection of prostate (TURP) and radical prostatectomy specimens. A further 101 patients were diagnosed clinically, with no available histology. Given that patients were diagnosed over a subsequent two year period, it would be difficult to apply this nomogram to clinical practice, and is not directly comparable to the current study.

In addition to MRI, the ongoing search and development of novel prostate cancer biomarkers has been documented and could aid the development of new nomograms.

These markers, including the four kallikrein panel (4K), prostate health index (PHI, a panel of total PSA, free PSA and [-2]proPSA) and urinary prostate cancer gene 3 (PCA3) have been integrated into clinical nomograms to improve their accuracy, with accuracy reported in the range 0.73-0.80 on ROC analysis [30-32]. These assays have the potential to supplant PSA and PSAD, and how they will integrate into the diagnostic pathway along with MRI remains to be determined. However, we note that these assays are not freely available in all centres, including in the United Kingdom, from which this study group arises.

The strengths of the present study include the fact it is a large, prospective study, involving 615 patients. MRI was reported prospectively by a single urologist, blinded to clinical details, avoiding reporter bias. Our study uses TPSB as a reference standard, interrogating all

sectors of the prostate and avoiding the inherent sampling error associated with transrectal biopsies.

MRI reporting used PI-RADS v1. PI-RADS has changed since initial publication; in v1, T2, DWI and DCE sequences were considered equivalent, whereas in v2, DCE became a secondary sequence, used to delineate indeterminate PI-RADS 3 lesions [33]. This highlights the importance of the two primary sequences used in this study. Furthermore, studies have shown similar accuracy between both v1 and v2 [34, 35].

We note potential sources of bias. Firstly, the ellipsoid method was used for the calculation of prostate volume. For the purposes of this nomogram, our aim was to create a user friendly prediction tool with straightforward calculations. Formulaic prostate volume calculation is quick, requires little training and does not require further software, making data input very accessible. We have found that PSAD utilising this volume calculation method provides an improvement in the prediction of TPSB outcomes over total PSA alone [23].

While clinical details were blinded during MRI reporting, the study is prone to a learning curve, as MRI scans were re-reviewed with histology results. However, our published B-MRI series found little learning curve effect [13]. For this reason, active surveillance patients were excluded from our cohort. Our protocol for the reporting of active surveillance patients precludes the blinding of clinical details. When reporting such patients, our radiologist was both aware of the clinical details and previous histology, and able to compare new MRIs with previous imaging. In addition, many patients undergoing active surveillance did not go on to have biopsy after MRI; for example, patients with stable PSA

and negative MRI may have biopsies deferred, skewing the reference standard availability in this set of patients.

Furthermore, after the initial 400 cases in our cohort, patients were given the choice to proceed to TPSB, based on MRI results, potentially adding bias. We performed a sensitivity analysis to assess for any variations between the initial 400 patients versus the entire cohort. Results were similar, albeit with slightly weaker associations, when limiting analyses to these first 400 patients. The influence of informed patient decision making was small, represents current urological practice and is justifiable based on our initial results.

Finally, this nomogram requires external validation to be used in different cohorts. Our population is predominantly Caucasian, presenting with rising PSA and lower urinary tract symptoms; therefore, benign patients often have low PSAD due to increased prostate volume. It may not be representative of populations at other institutions, which may include screened patients with lower PSA values and prostate volumes.

Conclusions

We demonstrate an MRI-derived nomogram for the prediction of TPSB outcomes. Our nomogram shows good discrimination for any (87%) and significant (92%) prostate cancer on internal validation and supports the combination of pre-biopsy MRI findings and clinical risk factors. It can be used in clinic for patient counselling as part of the biopsy decision-making process.

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Figure Legends

Figure 1: (a) MR-based Nomogram predicting any prostate cancer on transperineal prostate biopsy. Instructions: To obtain nomogram-predicted probability of prostate cancer (PCa), patient values are located for each variable. A vertical line is drawn to the 'Points' axis to determine the number of points attributed to each variable. The points are added up for all variables. The sum is located on the 'Total Points' line to show the individual's probability of cancer on transperineal prostate biopsy on the 'PCa probability' line; (b) calibration curve of MR-based nomogram. Perfect prediction corresponds to the dashed 45° line. Points estimated above the 45° line represent nomogram underprediction, whereas points below the 45° line correspond to nomogram overprediction. The nonparametric, smoothed dotted curve represents the relationship between predicted probability and observed frequency of PCa at transperineal prostate biopsy across the entire cohort. The solid curve was bias-corrected by bootstrapping using 200 resamples.

Figure 2: (a) MR-based Nomogram for predicting significant prostate cancer (Gleason 4 or 3+3 (MCCL ≥ 6 mm)) on transperineal prostate biopsy; (b) calibration curve of MR-based nomogram for significant prostate cancer. Instructions as per Figure 1.

Figure 1a
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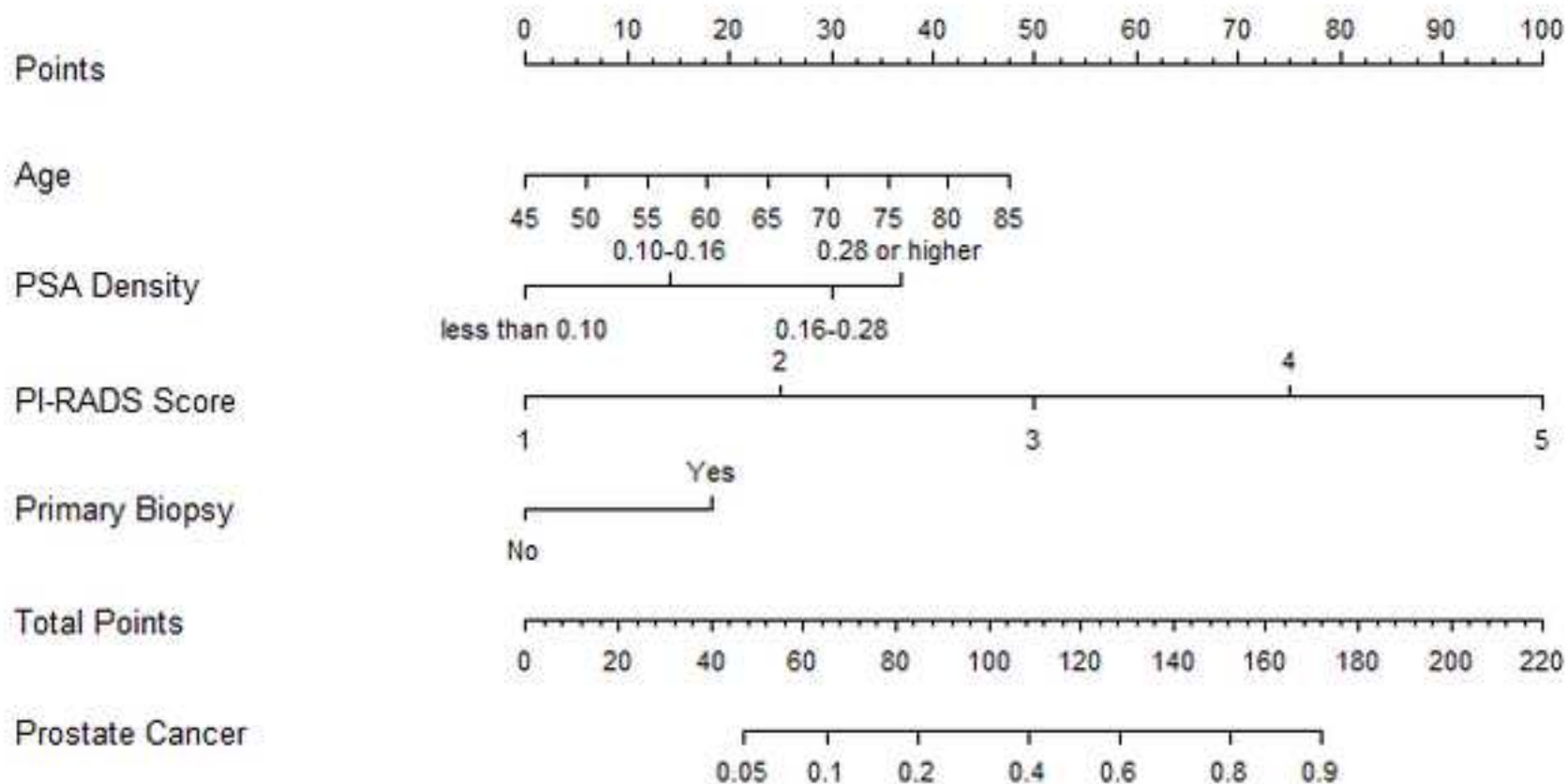


Figure 1b
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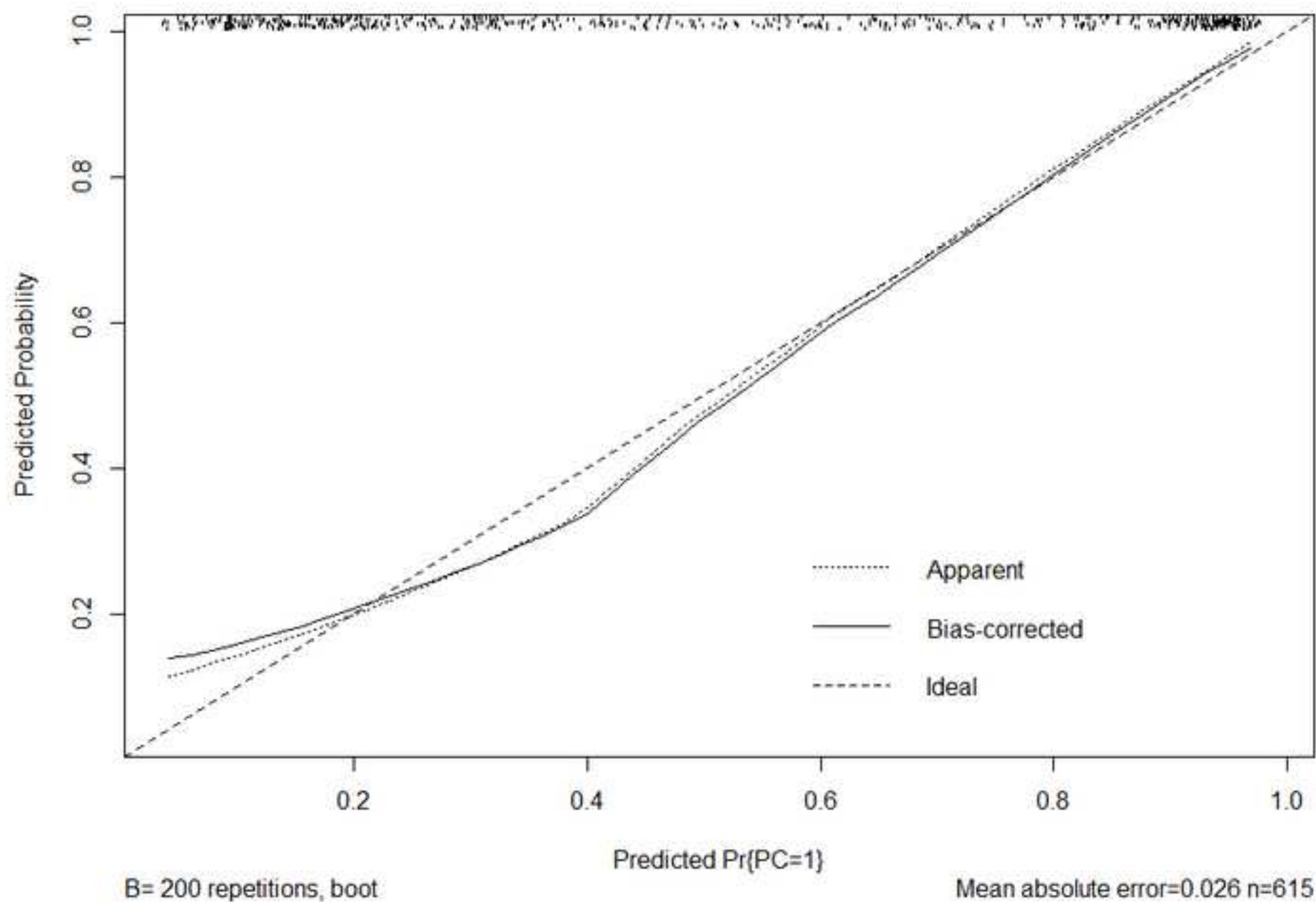


Figure 2a
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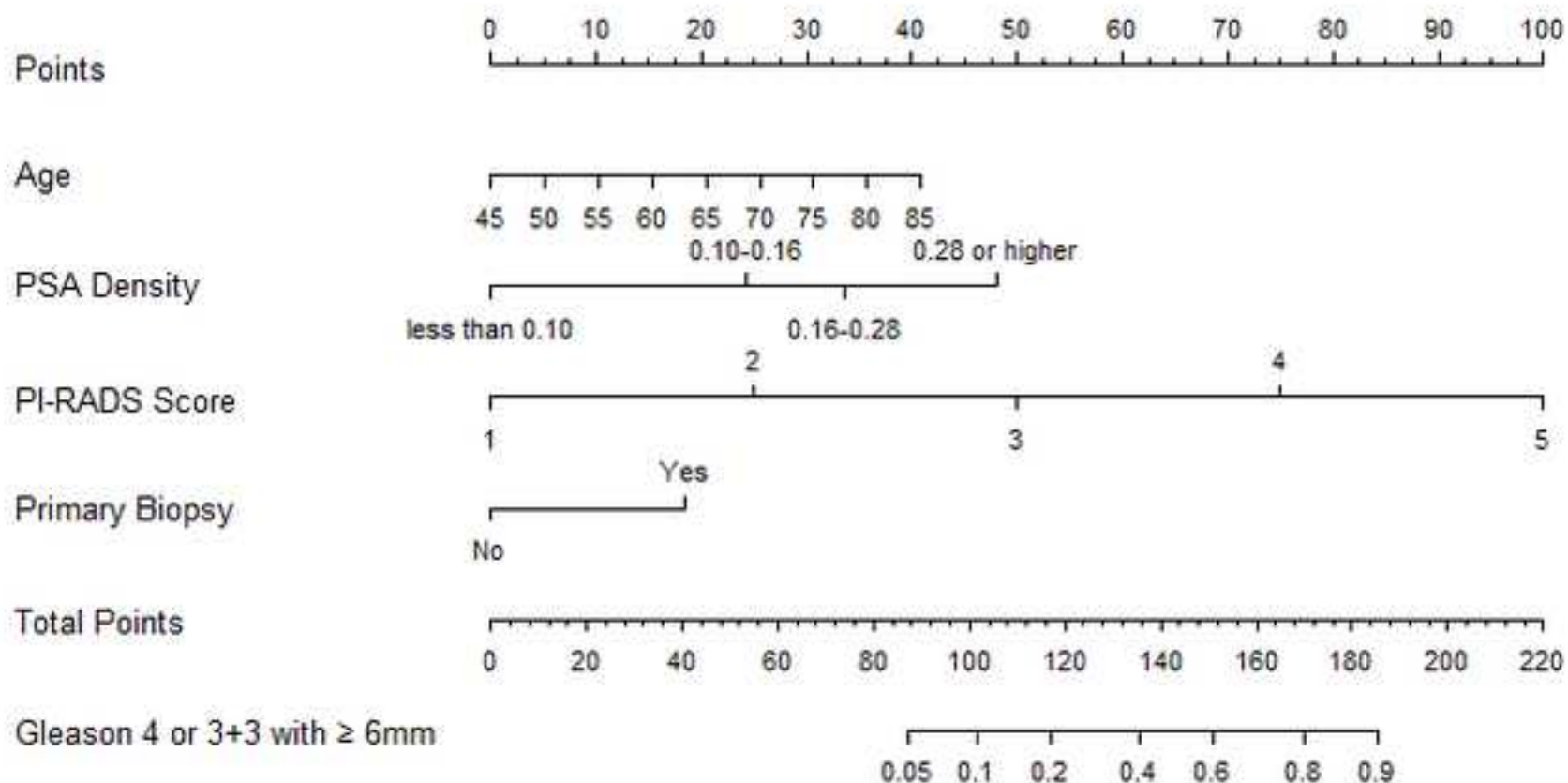


Figure 2b

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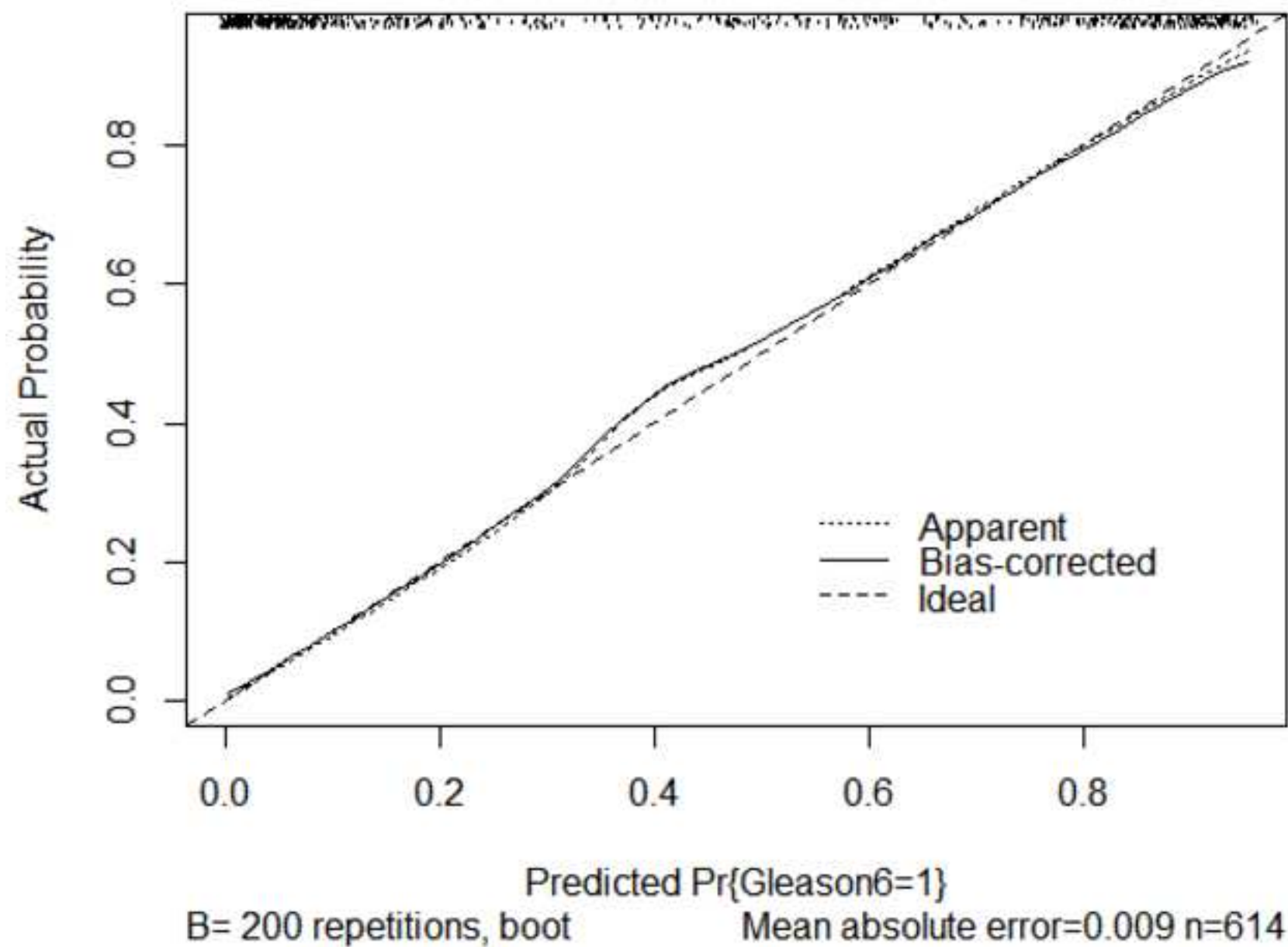


Table 1: Patient Characteristics

	All patients (n=615)	Prostate Cancer (n=317)	No Cancer (n=298)	<i>p</i> value
Age, Mean ± SD	65.4 ± 6.9	66.7 ± 6.9	64.1 ± 6.5	<0.0001
PSA, Mean ± SD	15.4 ± 39.2	20.6 ± 53.4	9.9 ± 9.2	0.0005
PSA Density, Mean ± SD	0.37 ± 2.03	0.58 ± 2.81	0.15 ± 0.14	0.0088
Primary Biopsy	484 (79%)	277 (87%)	207 (69%)	<0.0001

Table 2

Table 2: Univariable and Multivariable Associations of Predictor Variables for Any and Significant Prostate Cancer

Univariable Analysis				
	Any Prostate Cancer		Significant Prostate Cancer	
	OR (95% CI)	P	OR (95% CI)	p
Age	1.06 (1.03-1.09)	<0.0001*	1.07 (1.04-1.10)	<0.0001*
PSA	1.04 (1.02-1.06)	<0.0001*	1.06 (1.04-1.09)	<0.0001*
PSAD				
<0.10	-	<0.0001*	-	<0.0001*
0.10-0.16	2.11 (1.30-3.46)		3.75 (1.99-7.44)	
0.16-0.28	5.19 (3.20-8.57)		9.01 (4.91-17.59)	
≥0.28	10.37 (6.21-17.79)		24.22 (13.01-48.07)	
PI-RADS				
1	-	<0.0001*	-	<0.0001*
2	1.69 (0.64-5.29)		1.00 (0.33-38.35)	
3	3.09 (1.22-9.51)		6.00 (1.17-109.96)	
4	12.16 (4.83-37.36)		38.56 (7.97-694.81)	
5	79.58 (29.97-256.39)		179.23 (37.17-3230.92)	
Primary Biopsy				
No	-	<0.0001*	-	<0.0001*
Yes	3.04 (2.03-4.64)		3.75 (2.35-6.22)	
Multivariable Analysis				
	Any Prostate Cancer		Significant Prostate Cancer	
	OR (95% CI)	P	OR (95% CI)	p
Age	1.51 (1.13-2.01)	<0.0001*	1.05 (1.02-1.09)	<0.0001*
PSAD				
<0.10	-	<0.0001*	-	<0.0001*
0.10-0.16	1.87 (1.05-3.36)		3.57 (1.66-8.02)	
0.16-0.28	3.17 (1.74-5.77)		5.81 (2.76-12.42)	
≥0.28	4.26 (2.22-8.16)		12.26 (5.71-27.80)	
PI-RADS				
1	-	<0.0001*	-	<0.0001*
2	1.59 (0.54-4.61)		1.90 (0.29-37.38)	
3	2.84 (0.99-8.13)		5.61 (1.01-105.78)	
4	8.38 (2.94-23.90)		25.47 (4.87-471.35)	
5	43.12 (14.34-129.72)		91.52 (17.51-1694.02)	
Primary Biopsy				
No	-	<0.0001*	-	<0.0001*
Yes	2.16 (1.28-3.68)		2.68 (1.42-5.20)	

Table 3

Table 3: Numbers of biopsies performed and missed prostate cancer (any or significant) according to different MR-based nomogram-derived probability cut-offs

Probability (any cancer) cut-off (%)	Biopsies performed, n (%)	Biopsies not performed, n (%)	Any cancer missed, n	Significant cancer missed, n	For significant prostate cancer:			
					Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
5	588/615 (95.6)	27 (3.7)	4	1	99.6	6.9	40.4	96.3
10	550/615 (89.4)	65 (10.6)	11	2	99.2	16.7	42.7	96.9
15	504/615 (82.0)	111 (18.0)	20	3	98.7	28.6	46.4	97.3
20	456/615 (74.1)	159(25.9)	27	4	98.3	41.0	51.1	97.5
25	435/615 (70.7)	180 (29.3)	30	5	97.9	46.3	53.3	97.2
30	402/615 (65.4)	213 (34.6)	37	6	97.5	54.8	57.5	97.2

Table 4

Table 4: Percentage risk of significant and any (parentheses) prostate cancer (Gleason 4 or ≥6mm MCCL) in a 60 year old man with no previous prostate biopsy

60 years old		PSA Density			
		<0.10	0.10-0.16	0.16-0.28	>0.28
PI-RADS	1	<5% (<5%)	<5% (6%)	<5% (11%)	<5% (14%)
	2	<5% (9%)	<5% (15%)	7% (25%)	13% (31%)
	3	<5% (21%)	14% (33%)	20% (47%)	35% (55%)
	4	14% (42%)	36% (57%)	48% (71%)	66% (77%)
	5	37% (67%)	67% (78%)	77% (87%)	88% (>90%)

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23 June 2017

To the editor,

We wish to re-submit our manuscript entitled **“Towards a MRI-based nomogram for the prediction of transperineal prostate biopsy outcome: a physician and patient decision tool”** for consideration in Urologic Oncology: Seminars and Original Investigations.

We would like to thank you and the reviewers for the valuable comments and feedback which have allowed us to improve our manuscript. I have attached a detailed list of the changes that we have made and responses to each of the reviewers’ comments.

We confirm that this work is original and has not been published elsewhere nor is it currently under consideration for publication elsewhere. We declare no conflicts of interest.

All authors have read and approved the manuscript.

Thank you for your consideration of this manuscript,

Sincerely,

A handwritten signature in black ink, appearing to read 'Su-Min Lee', written in a cursive style.

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